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| APPLICATION NO.  | FILED DATE | FIRST NAMED INVENTOR | ATTORNEY DOCKET NO.         | CONFIRMATION NO. |
|--|------------|----------------------|-----------------------------|------------------|
| 09 546,269   | 04 10 2000 | Thomas Hunziker      | 17811-014 CIP (M-14<br>CIP) | 3066             |
| 30623  | 7590       | 05 01 2003           |                             |                  |
| MINTZ, LEVIN, COHN, FERRIS, GLOVSKY<br>AND POPEO, P.C.<br>ONE FINANCIAL CENTER<br>BOSTON, MA 02111 |            |                      | EXAMINER                    | WITZ, JEAN C     |
|  |            |                      | ART UNIT                    | PAPER NUMBER     |
|  |            |                      | 1651                        | 1 (              |
| DATE MAILED: 05 01 2003  |            |                      |                             |                  |

Please find below and/or attached an Office communication concerning this application or proceeding.

|                              |                 |                |
|------------------------------|-----------------|----------------|
| <b>Office Action Summary</b> | Application No. | Applicant(s)   |
|                              | 09/546,269      | HUNZIKER ET AL |
|                              | Examiner        | Art Unit       |
|                              | Jean C. Witz    | 1651           |

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION

## Status

1)  Responsive to communication(s) filed on 23 April 2002.

2a)  This action is **FINAL**.                    2b)  This action is non-final.

3)  Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

## Disposition of Claims

4)  Claim(s) 24-26, 28-30 and 32-40 is/are pending in the application.

4a) Of the above claim(s) \_\_\_\_\_ is/are withdrawn from consideration.

5)  Claim(s) \_\_\_\_\_ is/are allowed.

6)  Claim(s) 24-26, 28-30, 32-40 is/are rejected.

7)  Claim(s) \_\_\_\_\_ is/are objected to.

8)  Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

## Application Papers

9)  The specification is objected to by the Examiner.

10)  The drawing(s) filed on \_\_\_\_\_ is/are: a)  accepted or b)  objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

11)  The proposed drawing correction filed on \_\_\_\_\_ is: a)  approved b)  disapproved by the Examiner.

If approved, corrected drawings are required in reply to this Office action.

12)  The oath or declaration is objected to by the Examiner.

Priority under 35 U.S.C. §§ 119 and 120

13)  Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).  
a)  All b)  Some \* c)  None of:  
1.  Certified copies of the priority documents have been received.  
2.  Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.  
3.  Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).  
\* See the attached detailed Office action for a list of the certified copies not received.

14)  Acknowledgment is made of a claim for domestic priority under 35 U.S.C. § 119(e) (to a provisional application).  
a)  The translation of the foreign language provisional application has been received.

15)  Acknowledgment is made of a claim for domestic priority under 35 U.S.C. §§ 120 and/or 121.

**Attachment(s)**

1)  Notice of References Cited (PTO-892)  
2)  Notice of Draftperson's Patent Drawing Review (PTO-948)  
3)  Information Disclosure Statement(s) (PTO-1449) Paper Not(s)  
4)  Interview Summary (PTO-413) Paper Not(s)  
5)  Notice of Informal Patent Application (PTO-152)  
6)  Other

## DETAILED ACTION

### *Response to Arguments*

Applicant's arguments filed September 25, 2002 have been fully considered but they are not persuasive for the reasons set forth below.

### ***Claim Rejections - 35 USC § 103***

1. The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

2. This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 24-26, 28-30, and 32-40 are rejected under 35 U.S.C. 103(a) as being unpatentable over Baur combined with Lenoir et al. and Lenoir-Viale et al.

Applicants have amended the claims to modify the culture conditions of the claimed method to be performed in less than 5% human serum and to recite a specific

seeding density of the cells. Applicants have also submitted a declaration by one of the inventors, Dr. Limat.

Applicants argue that, as asserted by Dr. Limat at paragraph 5, "Applicants were the first to realized that such further dissection of the hair follicle was unnecessary.

Applicants' attention is directed to the disclosure of Lenoir at page 612, second column, the section labeled "Results". There, the reference states that "[w]hen freshly plucked hair follicles were deposited at the bottom of a culture dish and submerged into the culture medium for 5 days, narrow fringes of epithelial cells spreading on the dish could be observed (Fig. 2A) in the immediate vicinity of both upper and lower extremities of the outer root sheath of the hair follicle." The reference states that hair follicles were cut into two pieces, and the upper and lower halves were implanted into dermal equivalents and cultured. Large fringes of tissue had appeared around both upper and lower half of the implants and the area of the growing epithelium increased with time and eventually covered the dermal equivalents completely. Sectioning of the epithelium showed that it was stratified and "strikingly similar to interfollicular epidermis." "A granular layer with numerous keratohyaline granules and a horny layer were present. Moreover, a dense material evoking a basement membrane was deposited at the 'dermal-epidermal' junction and basal cells had a cuboidal shape, as normally found *in vivo*, but very rarely in culture. These results show that a stratified epithelium very similar to epidermis can be generated from hair follicles. The sites from which the epithelium originates (Fig. 2A) suggest that the outgrowing cells derive from the outer root sheath, as previously proposed by Weterings et al. (1980, 1981). Actually, in the absence of sebaceous

glands (see Fig. 1 that the plucked hair follicle is devoid of this appendage), the outer root sheath cells represent the vast majority of cells in direct contact with the culture substratum. Moreover, the fact that a similar epithelium was obtained from lower and upper halves of the hair follicle excludes the possibility that the tissue originated from contaminating interfollicular keratinocytes, since they never reached the lower part of the hair follicle. Since the morphology of the outer root sheath (Strauss and Matoltsy, 1977) contrasts strikingly with that of interfollicular epidermis, one must conclude that the culture conditions have provoked a morphological shift of the outer root sheath into a stratified epithelium resembling epidermis." (emphasis added.)

Therefore, Figure 2A shows the culture of an intact follicle and the reference provides the reasonable expectation of success that the dissected follicle used in the primary culture of Baur could be replaced with an intact follicle and still obtain the outer root sheath cells needed for the organotypic culture of step c). It would have been logically obvious to one of ordinary skill in the art at the time the invention was made that if the intact follicle produces the desired outer root sheath cells, it would reduce the time and cost required in the practice of the method of Baur.

Dr. Limat also asserts that the methods of the claimed invention now require a lower concentration of serum in both the primary and organotypic culture. Dr. Limat asserts that the lower serum concentration reduces the cost and decreases the risk of disease transmission. However, the disclosure of Baur at col. 5, lines 30-35, indicates that autologous serum is preferred and is taught to be included in a concentration of 0.5-60%, preferably 5-20% and most preferably 10%. In advocating the use of

autologous serum. Baur implicitly acknowledges that disease transmission is a concern of every practitioner in the art of human cell culture at the time the invention was made. Baur teaches that amounts of less than 5% are appropriate in the practice of the referenced invention. While greater amounts may be identified as being one of the preferred embodiments, the teaching of U.S. patent is not limited solely to its preferred embodiment. In fact, since the claims recite only "less than 5%", and the patent teaches that amounts of 5-20% are preferred, it would appear that the amounts claimed by Applicants and the amounts disclosed as preferred by Baur are very close.

Finally, the claims have been amended to recite specific seeding densities for the keratinocyte precursor cells in the organotypic culture. Baur teaches that these cells are seeded at concentrations of  $10^3$  –  $10^5$ , preferably  $5 \times 10^4$  to  $1 \times 10^5$ . While greater amounts may be identified as being one of the preferred embodiments ( $4 \times 10^5$ ), the teaching of U.S. patent is not limited solely to its preferred embodiment. The ranges claimed fall well within the ranges disclosed as providing a reasonable expectation of success of selection of keratinocyte precursor cells for the production of a skin equivalent.

Finally, Dr. Limat asserts in his declaration that the claimed method produces equivalents having "better stratification and a more normalized, stratified epidermis situation"; however, Applicants have provided no objective evidence to support this conclusion.

Therefore, absent objective evidence to the contrary, it would have been obvious to one of ordinary skill in the art at the time the invention was made to culturing the hair

follicle immediately after plucking since Lenoir et al. teaches that whole follicles can be used to the production of the equivalent. All that is required is a reasonable expectation of success, skipping the dissection/cutting step would not be expected to interfere with the expected outcome of the disclosed invention, i.e. the production of an epidermal equivalent. Ranges of serum and cell seeding densities claimed fall well within the ranges disclosed by Baur as appropriate for the practice of the invention.

***Conclusion***

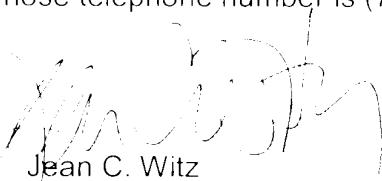
**THIS ACTION IS MADE FINAL.** Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Jean C. Witz whose telephone number is (703) 308-3073. The examiner can normally be reached on 6:30 a.m. to 4:00 p.m. M-Th and alternate Fridays.

• If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Wityshyn can be reached on (703) 308-4743. The fax phone numbers for the organization where this application or proceeding is assigned are (703) 308-4242 for regular communications and (703) 308-4242 for After Final communications.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to the receptionist whose telephone number is (703) 308-0196.



Jean C. Witz  
Primary Examiner  
Art Unit 1651